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Journal of Clinical Chemistry

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Review Article

Novel Advances and Recent Updates in The Crosstalk Between Neuroplasticity and Addiction

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Received date: September 06, 2022; **Accepted date:** September 16, 2022; **Published date:** November 19, 2022.

Citation: Ryan Varghese, Niraja Soman, Dileep Kumar. (2022). Novel Advances and Recent Updates in The Crosstalk Between Neuroplasticity and Addiction, *Journal of Clinical Chemistry*, 1(1); DOI: 10.31579/2835-8090/005.

Abstract

Undisputedly, the brain is the most complex organ in the human body, especially due to the paucity of understanding of its normal functioning and pathophysiology. However, the brain is characterized by its unique ability, called neuroplasticity, which facilitates the addiction and deaddiction of various habits or substances. The term 'neuroplasticity' is often used to describe the brain's ability to precipitate structural and functional changes, in response to particular experiences. While the neuroplastic nature of the brain helps in learning new languages and mastering demanding sports, it can also result in addictive disorders from substance abuse or detrimental habits. With recent advancements in the understanding and subsequent development of treatment modalities, there has been significant progress in rehabilitation and management of problems stemming from addiction. This article aims to review the various novel advancements devised for modifying neuroplasticity, to combat addiction to substance abuse.

Keywords: neuroplasticity; addiction; substance use disorders; treatment interventions; novel methods

1. Introduction

Since time immemorial, clinicians have regarded detoxification as the treatment for most kinds of addiction. However, detoxification is the mere removal of the drug from the body and symptomatic treatment of withdrawal symptoms. Over three decades ago, animal models and eventually human trials have demonstrated that the effect of the addiction lasts long after the termination of drug use. Thus, this helped to understand the neurological effect of addiction and is now regarded as a disease of neuroplasticity [1]. In general, addiction is a memory trace that manifests itself by the reflexive activation of brain circuits, particularly the reward system, which serves as a motivation for the user to repeat or resume drug abuse when related cues are present. Generally, the risk of addiction formation is attributed to those drugs that can potentially stimulate the reward system. However, the susceptibility to this addiction formation is a byzantine process and is an interplay of a complex set of factors, including several hereditary and environmental factors. Among various neurotransmitters and neuronal circuits, the key player in addiction formation and progression is the dopamine circuits which are stimulated by the various substances abused by people. This has been further directly and/or indirectly corroborated by various animal models and human brain imaging investigations. Although all users of a drug tend to experience fairly similar effects, only a small fraction of users progress to the point of compulsive use or addiction [2, 3]. The most prevalent types of neuroplasticity include tolerance accompanied by physical dependence and compulsive drug-seeking behavior.

Tolerance or physical dependence is a more prevalent type of neuroplasticity. Tolerance is generally observed as the reduced effects arising from a dose given repetitively, while physical dependence (not addiction) is characterized by withdrawal symptoms upon abrupt termination of medication. Reportedly, most people experience similar plasticity issues upon long-term medications, especially for chronic ailments. The second subset of neuroplasticity is represented by compulsive drug-seeking behavior. Generally, most drugs that can directly engage the reward system can result in learning, which directs the user to repeat actions that further reinforce the rewards of the drug. This type of neuroplasticity is characterized by its stability and prolonged and even permanent effects. With the usage of an addictive substance, more dopamine is released, compared to receiving natural rewards and this release tends to increase with time, rather than decrease as it would in natural rewards. Thus, it explains the stability and permanence of this kind of neuroplasticity [4]. Thus, the advent of theranostic devices and interventions that could deepen our understanding of neuroplastic alterations, while helping to substantiate its role in the development of

treatment protocols, would serve as a potential tool in combating various types and stages of addiction. This article would provide a bird's eye-view of novel advancements in clinical therapeutics in the recent years, while commenting on their utility and applicability of the same.

2. Novel methods to alter neuroplasticity in addiction medicine

Drug addiction has grown to become one of the greatest challenges worldwide. In India, cannabis and opiate addiction have been considered the most common form of addiction [5]. Addiction may be defined as a chronic brain dysfunction that results inperforming compulsive and obsessive behavior, to obtain the 'reward' that follows the abuse of any substance. This addiction is often characterized by high levels of dopamine, which accounts for the pleasant effect experienced during or after substance abuse [6, 7]. Additionally, in the case of addiction formation, neuroplasticityplays an imperative role in the development and maintenance of maladaptive behavior [6]. Neuroplasticity is often defined as the ability of the brain to develop newer connections and/or reorganize existing connections, usually in response to an experience or achanging environment [8]. This fundamental characteristic forms the rationale behind the development of rehabilitation programs [6]. Thus, knowledge and understanding of neuroplasticity have substantiated the potential utility of neuroplasticity as addiction medicine. Additionally, this has further aided in the developmentof various interventions that target the promotion of neuroplasticity. Some of the potential interventions have been elucidated below.

2.1. Non-invasive brain stimulation (NIBS)

Non-invasive brain stimulation (NIBS) is a technology that facilitates axon stimulation to initiate an action potential employing magnetic pulses or low-level electric pulses, without cranial penetration [9]. Generally, NIBS uses transcranial magnetic stimulation (tMS) and transcranial electrical stimulation (tES) to be employed as a theranostic tool against addiction medicine, especially substance use disorders (SUDs). tES is an umbrella term that encompasses several techniques based upon the level of the electric field applied. *Au contraire*, tMS induces small electrical currents in the cerebral cortex in either single, paired, or repetitive pulses [10]. Additionally, tMS also has several ancillary applications including the assessment of the integrity of the intracortical neuronal pathways, and monitoring of brain plasticity, which helps to derive important information on the effects of drug abuse [10, 11], devising interventions on neuroplasticity [12], and mapping of intracranial connections between different parts of the brain [13, 14], to list a few. However, these neuroplastic alterations are unique for each drug abuser, and these differences prevailing between individuals form the basis of efficient drug action. In such cases, tMS canbe employed to detect these alterations and to provide a treatment regimen, tailored to the needs of the patient. Therapeutically, both tMS and tES can be used to alter synaptic plasticity by precisely targeting the prefrontal cortical areas in reward processing. In addition, this would help alter the tendency of the brain to identify cues. Consequently, this will prevent the activation of the reward pathway in the brain, further reducing the craving for the particular drug. Thus, this would also prevent patient relapse after discontinuation of the abused substance [15]. Although these NIBS techniques appear to show promising results in improving the degree of recovery from SUDs, the variability in the results obtained from tMS and/or tES studies makes it difficult to reach a consensus.

Deep Brain Stimulation (DBS)

The first and second stages of addiction formation generally include intoxication and tolerance respectively. This reward circuit encompasses the forebrain, hypothalamus, and ultimately the nucleus accumbens (NAc), which are imperative for facilitating the reward [16]. To date, a broad spectrum of interventions, such as psychotherapy, drug therapy, and behavior modification, have been studied and reported to alleviate addiction, at different stages. However, these aforementioned modalities suffer from a high relapse rate ofabout 50-70%, which limits their utility in combating the latter [17].

Therefore, a much promising and potential intervention includes the application of the Deep-brain stimulation (DBS) technique. DBS is a method by which a device is surgically implanted in a particular part of the brain, which further ensures the delivery of electrical impulses. Furthermore, the DBS method is reversible and is regarded as a much safer alternative to brain neurosurgery. In recent years, numerous preclinical studies as well as a few clinical trials have been conducted to validate its efficacy in mitigating addiction. Due toits central role in the processing of pain and pleasure in the brain, NAc has been accepted as the primary target in most clinical studies [17, 18]. A recent study by Kuhn *et al.* included six patients with severe alcohol addiction who were subjected to high-frequency NAc DBS. Subsequently, the patients showed a marked decrease in craving and alcohol consumption, corroborating the utility of NAc DBS to have a positive effect in managing addiction [19]. However, despite numerous animal and clinical studies, the role and mechanism of NAc in devising an efficient DBS regimen remainunclear. Although the results are highly promising, further studies and clinical trials need to be conducted to elucidate their exact mechanism of treatment, as well as to prove their safety and efficacy. Furthermore, DBS is an invasive method, which thus poses potential risks of hemorrhage and infection. In this regard, the NIBS methods might prove to be safer than DBS. Moreover, DBS has been reported to potentially alter the patient's personality, which calls for the addressing of several ethical considerations and regulatory restraints [20]. However, these ethical hurdles and regulatory impediments are beyond the purview ofthis review.

2.2. Cognitive-behavioral therapy (CBT)

CBT is a psychotherapy that has been demonstrated to be effective against a multitude of problems, and addiction is not an exception. CBT is known to target environmental triggers for substance use and abuse, while simultaneously delivering training on coping skills that help achieve complete abstinence [21]. The two main components of CBT include the analysis of thoughts, feelings, behaviors, and skill training to develop active and positive behavior. Skills training involves interventions to enhance motivation while coping with craving, emotion regulation, self-monitoring, and relaxation, to list a few. CBT isone of the most commonly used therapies in the management of alcohol and substance abuse addiction. The most common example of CBT is cognitive inhibition of craving, which further helps the patient cope with withdrawal symptoms [22]. CBT works by analyzing the relationship between the patient's thoughts and thinking, and its subsequent reinforcement in the modulation of addictive behavior. False and negative beliefs are first identified and then reconstructed to yield positive results. Most CBT protocols have multiple components as parameters and largely comprise self-regulatory behaviors, that are most often self-reported by the patient or measured by third-party observations. As a result, there are many variables and perspectives involved in the measurement and validation of the effectiveness of this technique. Furthermore, owing to the differences in patient characteristics, no fixed standard could act as a reference or yardstick for the measurement of patient improvement. Hence, a fixed medicine-based approach with fixed parameters needs tobe adopted to achieve homogeneity in the conducted preclinical and clinical studies. Additionally, this will aid in achieving a consensus regarding the effectiveness of CBT as anaddiction medicine

Physical Exercise

One of the most difficult and major hurdles in overcoming drug addiction is relapse. During abstinence, there is an activation of neurobiological pathways that induce a craving for the drug. The chronic craving pathway is the result of a reduction in dopamine D2 receptors in the brain cortex. Consequently, this reduction precipitates a reduction in dopamine activity, which leads to anhedonia. Anhedonia is a common withdrawal symptom, which is the inability to feel pleasure, while concurrently losing interest

in activities that were known to give pleasure to that individual. Furthermore, anhedonia induces a craving for dopamine, which causes relapse in the patient [6, 23]. Thus, to prevent this relapse, physical exercise is recommended as a complementary therapy for patients during their rehabilitation. Any activity that results in body movement and requires energy expenditure can be deemed as physical exercise. This exercise is associated with self- regulation processes such as inhibitory behavior and decision-making, which in turn aid in promoting neuroplasticity [16, 24]. Additionally, it also helps to reduce dopamine-induced cravings. These neuroplastic changes are expected to inhibit drug-seeking

behavior and impulsivity for drug consumption. Reports from various preclinical studies have corroborated the neurobiological mechanisms induced by exercise, validating its efficacy as a therapeutic measure against drug addiction [25, 26, 28]. A recent study by Robinson *et al.* examined the exercise-induced changes in male (n=16) and female (n=16) Lewis rats. These rats were grouped mainly into sedentary and exercise groups. Rats grouped in the exercise group were placed on a treadmill at 10 m/min, 5 days a week for 6 weeks. On the contrary, the rats grouped into the sedentary group were kept in their respective cages. Subsequently, the rats were euthanized, following which an *in vitro* autoradiography was performed on the brains of the rats from both groups, at the end of the 6weeks. The study reported that exercised rats had 18% to 21% lower dopamine levels compared to rats in the sedentary group. Furthermore, no significant differences were observed between male and female rats in the binding of dopamine to D1 and D2 receptors.

Both sexes showed lower dopamine binding to the D1 receptor and higher dopamine bindingto the D2 receptor. These differences in dopamine receptor binding between the groups, elucidate the neuro-mechanism by which exercise is capable of reducing drug-seeking behavior [20]. The results derived from various similar studies have corroborated the fact that aerobic exercise, leads to changes in the mesolimbic pathway, that mediates exercise-induced attenuation of drug addiction. However, the authors opine that further studies are required to provide concrete evidence on the effectiveness of exercise in preventing drug relapse.All of the aforementioned treatment methods have shown promising results and have the potential to be widely used as addiction medicine in the near future. However, more clinical studies and standardized protocols for treatments are needed before they can be used safely and effectively for treatment.

2.3. Stem cell therapy as addiction medicine

Stem cells are generally referred to as undifferentiated or partially differentiated cells, with the potential to differentiate into various types of cells or proliferate indefinitely to produce more stem cells. These stem cells can be derived from the human umbilical cord, bone marrow, adipose tissue, and amniotic fluid [27]. Mesenchymal stem cells (MSCs) show various properties that are superior to those of other types of stem cells. These featuresinclude rapid replication, and limited lifespan in an *in vitro* culture, which further protects them from malignant transformation post transplantation. However, the requirement of a large number of MSCs to deliver optimal efficacy of the treatment can be a major limitation [28].

Substances with the potential for abuse generally have an anatomical and physiological impact on the brain and body. They exert dopaminergic effects on the brain, thus creating cell cycle pathways that stimulate cravings for the substance, ultimately leading to relapse of the drug abuse. In such cases, stem cells can be employed to alter these pathways and reverse theneuroplastic changes that have occurred in the brain during addiction formation, to prevent relapse. A study conducted by Rafaiee *et al.* tested the effects of bone marrow-derived MSCson hippocampal damage resulting from alcohol abuse. The toxicity of ethanol after alcohol abuse disturbs the hippocampus, while drug abuse leads to neuroinflammation and neurodegeneration in its gyri. The study identifies neural stem/progenitor cells (NSPCs) as the most affected cell population in addiction. To tackle this, MSCs were used as therapy in alcohol abused rats. Previous studies on MSCs corroborate their utility in neurological disorders, due to their safety profile and their ability to cross the blood-brain barrier (BBB).

Injection of a single dose of MSCs into the alcohol-associated dementia model demonstrated improvement in learning and memory function. Furthermore, the transplanted MSCs have also reported decreased 24-hour alcohol intake and interception in a relapse of alcohol drinking in induced alcohol deprivation models. In addition, it has also reported a reduction in the incidence of neuroinflammation and an increase in the neurogenesis of cells in the hippocampal region [29].

Another study by Israel *et al.* aims to understand the blockade of relapse in alcohol drinking by MSC therapy. The study employed female Wistar rats, raised specifically for their alcoholpreference. Furthermore, MSCs labeled with a carboxyfluorescein succinimidyl ester (CFSE)marker were used. The control animals received a single dose of the vehicle. *Au contraire,* Test group 1 had been given continuous access to 10% v/v alcohol and water for 73 days followed by access to 10% v/v alcohol and 20 % v/v water for the next 27 days.

Subsequently, these rats received a single intracerebroventricular (ICV) injection of the vehicle and bone marrow-derived MSCs and/or adipocyte tissue-derived MSCs into their leftlateral ventricle. Furthermore, it was also given access to alcohol for another 10 days.

Another parallel test group 2 was used to determine the effect of MSCs in alcohol-deprived rats in which rats received free access to 10% v/v alcohol for 73 days followed by 13 days offree choice of 10% v/v alcohol and 20 % v/v water. Finally, test group 2 was deprived of alcohol for 14 days and then administered a single dose of MSCs via ICV on the fourth day of alcohol deprivation. Alcohol was again offered at the end of 14 days and alcohol intake was determined in the first 60 minutes. Data was expressed with the help of two-way ANOVA. Results of the study showed that the MSCs survive and attach to rat cerebral ventricles and reduced the 24-hour alcohol intake by 50% during the 10 days of alcohol

deprivation. Furthermore, the MSCs were viable for a long period, reducing the need for subsequent dosing [30]. These aforementioned studies demonstrate a promising future for the potential utility of stemcell therapy in alcohol addiction. Additionally, it has been reinforced by its safety profile, efficacy, and rapid recovery rate. Furthermore, these studies on alcohol addiction can also beextrapolated for the treatment and mitigation of other forms of drug abuse in the near future. However, the results from preclinical and clinical studies are of paramount importance to explore their therapeutic indications, contraindications, and side effects, before translating this research from bench to bedside.

3. Conclusions and future prospects

The human brain is plastic, which aids the brain to learn and unlearn things, and addiction is no exception. The neuroplastic alteration that has detrimentally occurred in the brain during drug addiction formation and sustenance, could thus be reversed using various theranostic interventions. These interventions could not only diagnose the alterations in brain neuroplasticity but could also act as therapeutic devices for the treatment and reversal of the same. Over the decades, several such novel techniques have been devised and tested for the treatment of addictionand the symptoms that result from the latter. However, the authors believe that these studies should be corroborated and validated by several pre-clinical and clinical studies. This would further reinforce the trust of physicians, clinicians, and the scientific community in these novel techniques while paving way for future interventions.

4. Conflict of Interest

The authors declare that there is no conflict of interest.

5. Funding Information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

6. Author Contributions

Ryan Varghese: Conceptualization, Resources, Data Curation, Writing-Original Draft, Writing-Reviewing and Editing, Visualization, Project Administration

Niraja Soman: Writing-Original Draft, Writing-Reviewing and Editing, Visualization

Dileep Kumar: Resources, Supervision, Project Administration

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